



Hereditary Angioedema Treatments Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS AND DOSAGES

Drug	Manufacturer	Indication(s)
C1-INH [Human] (Berinert®) ¹	CSL Behring	Treatment of acute HAE facial, laryngeal, or abdominal attacks in adolescents and adults Safety and efficacy for prophylactic therapy have not been established
ecallantide (Kalbitor®) ²	Dyax	Treatment of acute HAE attacks in ages ≥ 12 years
icatibant (Firazyr®) ³	Shire	Treatment of acute HAE attacks in ages ≥ 18 years
pdC1-INH [Human] (Cinryze®) ⁴	Shire	Routine prophylaxis against angioedema attacks in adolescents and adults HAE
rhC1-INH [recombinant] (Ruconest®) ⁵	Salix	Treatment of acute attacks in adult and adolescent patients with HAE Limitation of use: effectiveness has not been established in HAE patients with laryngeal attacks

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema

OVERVIEW

Hereditary angioedema (HAE) is a rare dominant, autosomal genetic disorder that affects between 6,000 and 30,000 individuals in the United States.⁶ Patients with HAE have low levels of endogenous or functional C1 esterase inhibitor (C1-INH). HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous (SC) or submucosal edema involving the skin or mucosal tissues of the upper respiratory and gastrointestinal (GI) tracts. Although swelling can resolve spontaneously in several days, without treatment, laryngeal edema may be fatal and the pain of GI attacks can be incapacitating. Symptoms can begin as early as 2 years of age and persist throughout life with unpredictable severity and frequency of attacks. It is thought that minor trauma and stress can lead to an attack; however, many attacks can occur without any apparent trigger.

There are two types of C1-INH deficient HAE. The most common type (Type I), in which the body does not produce enough C1-INH, occurs in about 85% of patients.⁷ Type II HAE is characterized by the presence of normal or high levels of a dysfunctional C1-INH.

The complications of HAE do not respond well to the usual therapies for mast-cell mediated angioedema, including antihistamines, epinephrine, and glucocorticosteroids, necessitating the establishment of an accurate diagnosis.⁸ Complement C4 level antigenic levels should be measured in any patients suspected of having HAE. If the C4 level is decreased, or in cases where it is normal, but most or all of the clinical criteria listed above are met, C1-Inhibitor antigenic and functional levels should be tested to confirm the HAE diagnosis.

HAE prophylaxis is needed to reduce potential edema caused by a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (long-term prophylaxis). The 2013 U.S. Hereditary Angioedema Association (HAEA) consensus document recommends short-term prophylaxis prior to medical, dental, or surgical procedures.⁹ The need for long-term prophylaxis should be made based on attack frequency, attack severity, comorbid conditions, access to treatment, and patient experience and preference. Because disease severity may

change over time, the need for continued long-term prophylaxis should be assessed periodically. In addition, patients on prophylactic therapy should also have access to on-demand treatment for acute attacks.

Traditionally, 17-alpha-alkylated androgens (e.g., danazol) have been used for HAE prophylaxis. This oral anabolic androgen is associated with many adverse effects and is contraindicated in pediatrics and pregnancy/lactation. The HAEA evidence-based recommendations advise against the use of anabolic androgens for long-term prophylaxis for patients who are intolerant to anabolic androgen or if the effective dose exceeds the equivalent of 200 mg danazol per day.¹⁰ Also, failure of androgen therapy should not be a prerequisite to prophylactic C1-INH therapy. Antifibrinolytic agents (e.g., tranexamic acid and aminocaproic acid) have also been used to prevent HAE attacks, but have limited efficacy and significant toxicity. C1-INH (Cinryze) has demonstrated effectiveness in short- and long-term prophylaxis.

Goals of HAE treatment include reducing morbidity and mortality. Treatment should be individualized and provide optimal care and quality of life to the patient. The 2012 Hereditary Angioedema International Working Group (HAWK) evidence-based recommendations and 2012 World Allergy Organization evidence-based recommendations consider C1-INH (Berinert, Cinryze, Ruconest), ecallantide (Kalbitor), or icatibant (Firazyr) all first-line agents in HAE treatment and support patient access to at least one of these medications.^{11,12} No one agent is recommended over another. Fresh frozen plasma (FFP) has been used in the absence of these agents with some success. Antihistamines, corticosteroids, or epinephrine have little or no clinical benefit for treatment of HAE. In 2013, a joint task force representing members of the American Academy of Allergy, Asthma, and Immunology (AAAAI); the American College of Allergy, Asthma, and Immunology (ACAAI); and the Joint Council of Allergy, Asthma, and Immunology also agreed with the above recommendations.¹³ A 2014 consensus report from the HAWK group on various types of angioedema also confirmed the above recommendations for treatment of HAE.¹⁴

PHARMACOLOGY^{15,16,17,18,19}

HAE is caused by mutations in the C1-INH located on Chromosome 11q and is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is not present; thus, during HAE attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms, including localized swelling, inflammation, and pain.

Berinert and Cinryze are pasteurized nanofiltered plasma derived concentrates of human plasma derived C1 esterase inhibitors (pdC1-INH). Ruconest is a recombinant analogue of C1-INH purified from the milk of transgenic rabbits. C1-INH acts by inhibiting kallikrein and suppress bradykinin formation resulting in increased plasma levels of C1-INH activity. All three C1-INH products are intravenously (IV) administered. Nontherapeutic proteins may be found in these products, but the impact of these proteins on the safety, such as immunogenicity, and efficacy is unknown.²⁰ Purity may also play a role

in immunogenicity; purity was highest for rhC1-INH (Ruconest) (98.6%), followed by the plasma-derived C1-INH, Berinert (97%), and Cinryze (89.5%).²¹

Ecallantide (Kalbitor) is a recombinant selective, reversible inhibitor of the plasma protein kallikrein. When ecallantide binds to kallikrein the conversion of HMS kinogen to bradykinin is blocked. Ecallantide is administered SC.

Icatibant (Firazyr) is a selective synthetic bradykinin B2 receptor antagonist. Icatibant has similar receptor affinity as bradykinin. Icatibant is administered SC.

PHARMACOKINETICS^{22,23,24,25,26}

Drug	Cmax	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
C1-INH [Human] (Berinert)	nr	nr	24	nr	nr
ecallantide (Kalbitor)	586 ng/mL	2-3	2	nr	renal
icatibant (Firazyr)	974 ng/mL	0.75	1.4	extensively metabolized by proteolytic enzymes to inactive metabolites	renal
pdC1-INH [Human] (Cinryze)	0.68-0.85 units/mL	2.7-3.9	56-62	nr	nr
rhC1-INH [recombinant] (Ruconest)	1.2-1.3 IU/mL	0.3	2.4-2.7	nr	nr

CONTRAINDICATIONS/WARNINGS^{27,28,29,30,31}

C1-INH products (Berinert, Cinryze, Ruconest) are contraindicated in patients with known serious hypersensitivity to the product. Hypersensitivity reactions may include hives, urticaria, tightness of chest, wheezing, and hypotension. If hypersensitivity reaction is suspected, C1-INH should be discontinued and treatment of hypersensitivity reactions should be carefully considered since symptoms are similar to HAE. Epinephrine should be prescribed for patients on C1-INH therapy for immediate use for acute severe hypersensitivity reactions.

Recombinant C1-INH (Ruconest) is also contraindicated in patients with a known allergy to rabbits or rabbit-derived products.

Use of ecallantide (Kalbitor) is contraindicated in patients with a known hypersensitivity to the product. Boxed warnings advise that ecallantide should only be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE. Patients should be observed for an appropriate period of time after administration of ecallantide.

There are no contraindications reported for icatibant (Firazyr).

Thromboembolic events (TE) have been reported in patients receiving C1-INH. Risk factors for TE include presence of an indwelling venous catheter, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptive, or androgen therapy, morbid obesity, and immobility.

Since plasma-derived C1-INH agents (Berinert, Cinryze) are derived from human blood, there is a potential for transmission of infection.

In addition to self-administering acute treatment with C1-INH (Berinert) or icatibant (Firazyr) for an acute HAE attack, patients should be instructed to seek immediate medical attention if laryngeal involvement is present.

The B2 receptor has been associated with cardioprotective effects of bradykinin and antagonism of this receptor has the potential to result in negative cardiovascular effects after acute ischemia. Icatibant (Firazyr) should be used with caution in patients with unstable angina and acute coronary ischemia and during the weeks following a cerebrovascular accident.

DRUG INTERACTIONS^{32,33,34,35,36}

No drug interactions studies have been performed with C1-INH (Berinert, Cinryze, Ruconest) or ecallantide (Kalbitor).

Icatibant (Firazyr) has the potential to increase the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors.

ADVERSE EFFECTS^{37,38,39,40,41}

Drug	Headache	Nausea	Rash	Vomiting	Abdominal Pain	Pyrexia	Injection Site Reaction	Diarrhea
C1-INH [Human] (Berinert)	7 (11.9)	7 (26.2)	3.5	2.3 (16.1)	7 (11.9)	nr	reported	0 (19)
ecallantide (Kalbitor)	11	13	3	6	5	5	3-7	11
icatibant (Firazyr)	reported	reported	reported	nr	nr	4 (0)	97 (25)	nr
pdC1-INH [Human] (Cinryze)	19	18	10	10	nr	5	reported	nr
rhC1-INH [recombinant] (Ruconest)	9	2	reported	nr	≥2	nr	nr	2

Other common adverse reactions reported for ecallantide (Kalbitor) include fatigue (12%), upper respiratory tract infection (8%), and nasopharyngitis (6%).

Because C1-INH (Berinert, Cinryze, Ruconest), is a therapeutic protein, there is potential for immunogenicity; however, no anti-C1 esterase inhibitor antibodies have been detected. There is no evidence that resistance develops with C1-INH treatment.

Presence of antibodies to ecallantide (Kalbitor) has been reported in approximately 20% of patients treated with ecallantide. Neutralizing antibodies were discovered in 8.8% of patients and did not lead to reduced efficacy. Rates of seroconversion increase with increased exposure to ecallantide and patients who seroconvert may be at increased risk of hypersensitivity reactions.

In clinical studies, anti-icatibant antibodies were detected in 4 patients, of which 3 patients had subsequent negative tests for antibodies. No change in efficacy or incidence of hypersensitivity was observed.

SPECIAL POPULATIONS^{42,43,44,45,46}

Pediatrics

The safety and efficacy of pdC1-INH (Cinryze) has not been established in patients < 18 years. Safety and efficacy of pdC1-INH (Berinert) have not been established in patients ≤ 12 years of age. Recombinant C1-INH (Ruconest) is indicated for use in adolescents and studied in patients ≥ 13 years.

Ecallantide (Kalbitor) is approved for use in patients ≥ 12 years of age. Data on the effectiveness of ecallantide in 12 to 15 year old patients, which showed similar drug exposure in adult and adolescent patients, were extrapolated to patients ≥ 16 years of age.

Safety and efficacy of icatibant (Firazyr) have not been established in patients < 18 years of age.

According to the U.S. Hereditary Angioedema Association, parents should discuss if one of the available HAE therapies may be an appropriate choice for use with their child and work with their prescriber to obtain access.⁴⁷

Geriatrics

The numbers of subjects ≥ 65 years of age were not sufficient in studies of pdC1-INH (Berinert, Cinryze), rhC1-INH (Ruconest), ecallantide (Kalbitor), or icatibant (Firazyr) to establish differing response from younger patients.

Pregnancy

Recombinant C1-INH (Ruconest) is Pregnancy Category B based on animal studies. Plasma-derived C1-INH (Berinert, Cinryze) is Pregnancy Category C since no animal data are available. Ecallantide (Kalbitor) and icatibant (Firazyr) are Pregnancy Category C.

An international consensus group, which included representation from the U.S., recommended the use of plasma-derived human C1-INH (Berinert, Cinryze) for acute treatment, short-term prophylaxis, and long-term prophylaxis in pregnant patients and stated that this should also be available during labor and delivery if needed.⁴⁸ Tranexamic acid or fresh frozen plasma (FFP) may be used for long-term prophylaxis if plasma-derived human C1-INH is unavailable. Data in this population using recombinant C1-INH (Ruconest) were not available at the time of this publication.

Hepatic Impairment

No dose adjustment of icatibant (Firazyr) is needed in patients with hepatic impairment.

Use of C1-INH (Berinert, Cinryze, Ruconest) in patients with hepatic impairment has not been evaluated.

No pharmacokinetic data are available for use of ecallantide (Kalbitor) in patients with hepatic impairment.

Renal Impairment

No dose adjustment of icatibant (Firazyr) is needed in patients with renal impairment.

Use of C1-INH (Berinert, Cinryze, Ruconest) in patients with renal impairment has not been evaluated.

No pharmacokinetic data are available for use of ecallantide (Kalbitor) in patients with renal impairment.

DOSAGES^{49,50,51,52,53}

Drug	Dosage	Availability
pdC1-INH (Berinert)	20 IU/kg IV at a rate of 4 mL/min Lower doses than 20 IU/kg should not be given May be self-administered with proper training A silicone-free syringe should be used for reconstitution and administration of Berinert	Lyophilized powder for reconstitution; 500 IU/10 mL single-use vial
ecallantide (Kalbitor)	30 mg SC administered as 10 mg/mL at 3 anatomical sites: abdomen, thigh, upper arm (site rotation not necessary); May repeat dose within a 24 hour period if attack persists HCP-administered	10 mg/mL solution single-use vial (3 per carton)
icatibant (Firazyr)	30 mg SC abdominally over at least 30 seconds; Additional doses may be administered at interval of at least 6 hours if inadequate response or symptoms recur; No more than 3 injections should be administered in 24 hours May be self-administered with proper training	30 mg/3 mL prefilled syringe
pdC1-INH (Cinryze)	1,000 units IV every 3 to 4 days at a rate of 1 mL/min (10 minutes) May be self-administered with proper training	Lyophilized powder for reconstitution; 500 units/5 mL single-use vial
rhC1-INH (Ruconest)	50 IU/kg IV over 5 minutes; May repeat dose if attack symptoms persist; Do not exceed 4,200 IU per dose; Do not exceed 2 doses in a 24 hour period Body weight < 84 kg: 50 IU/kg Body weight ≥ 84 kg: 4,200 IU (2 vials) May be self-administered with proper training	Lyophilized powder for reconstitution; 2,100 IU/25 mL single-use vial

HCP = health care professional; SC = subcutaneously; IU = international units; IV = intravenous

pdC1-INH (Berinert, Cinryze) and rhC1-INH (Ruconest) infusions should not be mixed with other medicinal products and should be administered in a separate infusion line.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human

participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in U.S., single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

C1 esterase inhibitors plasma derived (Cinryze)

A single randomized, double-blind, placebo-controlled multicenter cross-over study evaluated the safety and efficacy of pdC1-INH prophylaxis therapy to reduce the incidence, severity, and duration of HAE attacks.⁵⁴ This study enrolled 24 patients with HAE and a history of at least 2 HAE attacks per month. Age range in the study was 9 to 73 years. Patients were randomized to 1 of 2 treatment groups: either pdC1-INH prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis or placebo prophylaxis for 12 weeks followed by 12 weeks of pdC1-INH prophylaxis. Doses were given every 3 to 4 days, approximately 2 times per week. Patients kept a daily record of any new angioedema symptoms that were not present the previous day. The efficacy determination was based the comparison of the number of attacks during the 12-week period while receiving pdC1-INH versus placebo. Mean number of attacks was 6.1 for the study drug as compared to 12.7 for placebo ($p<0.0001$). Mean duration of HAE attacks reported was 2.1 days for pdC1-INH and 3.4 days for placebo. The number of days swelling reported was 10.1 for pdC1-INH and 29.6 for placebo. Mean severity was less with study drug, 1.3 versus 1.9, based on a 3-point scoring system (1=mild, 2=moderate, 3=severe).

C1 esterase inhibitors, plasma-derived (Berinert)

IMPACT-1: The safety and efficacy of pdC1-INH were evaluated in a placebo-controlled, double-blind, parallel-group, clinical study that enrolled 124 subjects who were experiencing an acute moderate to severe attack of abdominal or facial HAE.^{55,56} Age range of subjects was from 6 to 72 years. The time to onset of relief of symptoms was assessed based on patient questionnaires of individual symptoms and the severity of each symptom over time. Subjects were randomized into 3 groups to receive a single dose of pdC1-INH of 10 IU/kg or 20 IU/kg of body weight, or a single dose of placebo administered by slow intravenous infusion within 5 hours of a HAE attack. If sufficient relief of symptoms was not experienced by 4 hours after the infusion, study investigators had the option to give a blinded rescue dose as a second dose of pdC1-INH at 20 IU/kg for the placebo group, 10 IU/kg for the 10 IU/kg group, or placebo for the 20 IU/kg group. All subjects who received rescue medication were regarded as non-responders and the time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (including rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief. Subjects treated with pdC1-INH 20 IU/kg experienced a faster onset of symptom relief as compared to placebo (0.5 versus 1.5 hours, respectively; $p=0.0025$), regardless of the location of the attack (face or abdomen). The difference in the time to onset of relief from symptoms between the pdC1-INH 10 IU/kg group and the

placebo group was not statistically significantly different. Within 60 minutes after the administration of study medication, 62.8% of subjects in the pdC1-INH 20 IU/kg group reported onset of symptom relief versus 26.2% in the placebo group. The median time to complete resolution of symptoms was significantly shorter with pdC1-INH 20 IU/kg compared with placebo (4.9 versus 7.8 hours, respectively; $p=0.0237$). Approximately 30% of subjects required rescue medication in the pdC1-INH 20 IU/kg group compared to about 55% in the placebo group.

C1 esterase inhibitors, recombinant (Ruconest)⁵⁷

The safety and efficacy of rhC1-INH in the treatment of acute attacks in patients with HAE were demonstrated in a placebo-controlled, double-blind, randomized study (Study 1). Supportive evidence of effectiveness is provided by a double-blind, randomized, placebo-controlled study (Study 2).

Study 1: A double-blind, placebo-controlled trial that included an open-label extension evaluated the efficacy and safety of rhC1-INH 50 IU/kg in the treatment of acute HAE attacks in adults and adolescents (age range of 17 to 69 years).⁵⁸ Patients were randomized to receive rhC1-INH 50 IU/kg ($n=44$) or placebo ($n=31$). The primary efficacy endpoint was the time to onset of symptom relief as documented by patient-reported questionnaires. Primary efficacy was assessed by patient responses on a Treatment Effect Questionnaire (TEQ). Rescue medication was allowed for patients who had no symptom improvement at 4 hours after study drug administration, or earlier if life-threatening oropharyngeal-laryngeal angioedema symptoms occurred. If a patient required rescue medication prior to achieving beginning of relief of symptoms, the time to beginning of relief of symptoms recorded as the last time the TEQ was assessed prior to medication use. In the blinded phase, the median time to onset of symptom relief was statistically significantly shorter in patients treated with rhC1-INH compared to those treated with placebo (90 versus 152 minutes, respectively; $p=0.031$). Median time to minimal symptoms was 303 minutes in rhC1-INH group compared to 483 minutes in the placebo group ($p=0.078$). A lesser proportion of patients in the rhC1-INH group received rescue medication compared to the placebo group (11% versus 42%, respectively). Among patients who achieved relief within 4 hours, 27% ($n=4$) of patients in the placebo group had a relapse of their symptoms within 24 hours versus 3% ($n=1$) for the rhC1-INH group.

Data from planned subgroup analyses in U.S. patients showed that the median time to onset of symptom relief with persistence was 98 minutes for those receiving rhC1-INH ($n=22$) and 90 minutes for those receiving placebo ($n=16$). Median time to onset of symptom relief for non-U.S. patients receiving rhC1-INH ($n=22$) was 90 minutes and 334 minutes for those receiving placebo ($n=15$). In addition, analysis of gender subgroups suggested a greater treatment response in men than women. The median time to onset of symptom relief was 113 minutes for women receiving rhC1-INH ($n=28$) compared to women receiving placebo of 105 minutes ($n=19$). In men, these values were 75 minutes ($n=16$) and 480 minutes ($n=12$), respectively. No explanations for the regional or gender subgroup responses were found; however, it was noted that there was a larger-than-expected placebo response among U.S. women.

In Study 2 (North American controlled trial), patients ranging in age from 17 to 66 years were randomized to receive a single dose of either rhC1-INH 50 IU/kg ($n=12$), rhC1-INH 100 IU/kg ($n=13$), or placebo ($n=13$). The efficacy of rhC1-INH in the treatment of acute HAE attacks was demonstrated by significantly shorter time to onset of symptom relief based on the Visual Analogue Assessment Scores (VAS). A VAS decrease of at least 20 mm as compared to baseline with persistence of improvement at 2 consecutive time points was deemed as onset of symptom relief.

ecallantide (Kalbitor)⁵⁹

EDEMA-3: The safety and efficacy of ecallantide were assessed in a randomized, double-blind, placebo-controlled trial of 72 patients with HAE assigned to receive ecallantide or placebo for acute attacks. The primary efficacy endpoint was the measured with the Treatment Outcome Score (TOS), a measure of symptom response at 4 hours after dose administration; a value greater than 0 reflected an improvement in symptoms from baseline. The key secondary efficacy endpoint was the change from baseline in Mean Symptom Complex Severity (MSCS) at 4 hours after the dose was administered. Patients treated with ecallantide experienced a significantly greater TOS than patients treated with placebo (63 versus 36, respectively; $p=0.045$) and a significantly greater decrease from baseline in the MSCS than placebo (-1.1 versus -0.6, respectively; $p=0.041$). In addition, 36% of patients in the placebo group required medical intervention to treat unresolved symptoms within 24 hours compared to 14% in the ecallantide group.

EDEMA-4: The safety and efficacy of ecallantide were assessed in a randomized, double-blind, placebo-controlled trial of 96 HAE patients assigned to receive ecallantide 30 mg SC or placebo for acute attacks of HAE. The primary endpoint was the change from baseline in MSCS score at 4 hours, and the key secondary endpoint was TOS at 4 hours. Patients treated with ecallantide experienced a significantly greater decrease from baseline in the MSCS than placebo (-0.8 versus -0.4, respectively; $p=0.01$) and a significantly greater TOS than patients with placebo (53 versus 8, respectively; $p=0.003$). At 24 hours, patients treated with ecallantide also reported a greater decrease from baseline in the MSCS than placebo (-1.5 versus -1.1, respectively; $p=0.04$) and a greater TOS (89 versus 55, respectively; $p=0.03$).

icatibant (Firazyr)

FAST-1 & 2:⁶⁰ The efficacy and safety of icatibant 30 mg SC injection was evaluated in 2 phase 3 randomized, double-blind, controlled clinical trials in patients with HAE who presented within 6 hours of an acute attack with cutaneous or abdominal symptoms. In FAST-1, 56 patients received either icatibant or placebo; in FAST-2, 74 patients received icatibant or oral tranexamic acid 3 g once daily for 2 consecutive days. The primary efficacy endpoint in both trials was the median time to clinically significant relief of the index symptom, which was defined as the symptom (cutaneous swelling, cutaneous pain, or abdominal pain) with the highest score on the VAS measured prior to study drug administration. Abdominal pain was the index symptom for patients experiencing a combination of all 3 symptoms. In FAST-1, the time to clinically significant relief was not statistically significant between the icatibant group and placebo group (2.5 versus 4.6 hours, respectively; $p=0.14$). Although, as assessed by the patient and the investigator, the median time to first symptom improvement was significantly shorter in the icatibant group compared with the placebo group (0.8 hour versus 16.9 hours, respectively; $p<0.001$; and 1 hour versus 5.7 hours, respectively; $p<0.001$). In the FAST-1 study, 3 patients in the icatibant group and 13 in the placebo group needed rescue medication. In FAST-2, primary endpoint was reached in 2 hours for icatibant and 12 hours for tranexamic acid; the difference was statistically significant ($p<0.001$). No icatibant-related serious adverse events were reported.

FAST 3:⁶¹ In a randomized, placebo-controlled, double-blind, parallel-group study of 98 adults with HAE, patients received either a single dose of icatibant 30 mg or placebo by SC injection, given within 6 hours of onset of HAE symptoms. Patients with severe laryngeal attacks of HAE received open-label icatibant 30 mg. The primary endpoint was assessed with a VAS that included average assessments of skin swelling, skin pain, and abdominal pain. The median time to a response, defined as at least a 50%

reduction from the pretreatment composite 3-item VAS score, for patients with cutaneous or abdominal attacks treated with icatibant was 2 hours compared to 19.8 hours for placebo-treated patients ($p<0.001$). In addition, the median time to almost complete symptom relief was 8 hours for icatibant and 36 hours for placebo. Seven percent of patients in the icatibant group received rescue medication versus 40% in the placebo group.

SUMMARY

Hereditary angioedema (HAE) is a rare genetic disorder that results in low levels of endogenous or functional C1 esterase inhibitor (C1-INH). HAE is characterized by recurrent episodes of subcutaneous or submucosal edema involving the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. Accurate diagnosis of HAE due to C1INH deficiency is critical for proper treatment.

Plasma-derived concentrates of human plasma derived C1-INH (Berinert, Cinryze) and a recombinant analogue of C1-INH (Ruconest) are available as intravenous (IV) injections. Ecallantide (Kalbitor) is a selective inhibitor of the plasma protein, kallikrein, and is administered subcutaneously (SC). Icatibant (Firazyr) is a selective synthetic bradykinin B2 receptor antagonist and is also administered SC. All agents, with the exception of ecallantide, may be self-administered with proper training. Cinryze is FDA-approved for prophylactic use, while the remaining agents are indicated for treatment of HAE attacks. Thromboembolic events (TE) have been reported in patients receiving C1-INH. Although pasteurized and purified, since C1-INH agents (Berinert, Cinryze) are derived from human blood, there is a small potential for transmission of infection. Recombinant C1-INH (Ruconest) does not have this precaution. Icatibant (Firazyr) should be used with caution in patients with unstable angina and acute coronary ischemia and in the weeks following a stroke, due to the potential for negative cardiovascular effects. Headache and nausea are common adverse effects reported. Injection site reactions are most commonly reported with use of icatibant (Firazyr).

While all agents have established effectiveness in clinical trials, no head-to-head studies have been performed for the agents in the review. Per current clinical guidelines, C1-INH (Berinert, Cinryze, and Ruconest), ecallantide, and icatibant are all considered first line therapy for the treatment of HAE attacks; one agent is not preferred over another.

REFERENCES

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